PIN-2: A novel "immunopriming" polypeptide initiates a peripheral-systemic innate and adaptive immune response in an aggressive 4T1 murine mammary carcinoma model.

Introduction

PIN-2 is a novel immunomodulator derived from a transactivator protein that initiates activity by enhancing innate immune signaling ab initio.

Activation of systemic immunity in the host is required for effective cancer immunotherapy. Antitumor immune responses involve coordination across various cell types and tissues. Enhancement of peripheral innate immune signaling to coordinate adaptive immunity is an effective strategy to promote a protective antitumor immune response.

Experiments with PIN-2 demonstrate its rapid-onset of action and its ability to initiate monocyte differentiation into activated professional antigen presenting cells (DC-APCs) thereby linking adaptive immunity to induce an endogenous T-cell immune response.

Commercialized as an i.v. bolus demonstrates antitumor activity in a validated murine model of established poorly immunogenic mammary carcinoma (4T1) that synergizes with additional antitumor therapeutics that relieve T-cell mediated immunosuppression.

Next Generation Sequencing (NGS) of isolated CD4+ primary human monocytes following PIN-2 exposure in vivo reveals a pattern of gene expression indicative of innate immune activation evidenced by regulation of mRNA involved in cytokine signaling pathways, co-stimulatory ligands, and coding non-coding RNAs. The genetic signature of transcriptional changes induced by PIN-2 enables identification of novel immune-based biomarkers, targets for therapeutic intervention, and optimal design of rational combination immunotherapies.

Currently approved immunotherapies have limited clinical activity in patient populations with advanced solid tumors. The use of experimental next-generation cancer immunotherapies concurrent with conventional and targeted agents are being utilized in the identification of therapeutic approaches to improve clinical outcomes in patients with advanced solid tumors.

Background

- PIN-2 (Precision Immune Stimulant) drives the DC-APC innate immunity complex to stimulate T-cell mediated immunosuppression.
- Rationally designed artificial peptide derived from humanized sequences.
- PIN-2 demonstrated antitumor activity correlating with the degree of antigen affinity as evidenced by 2 clinically relevant mammary tumor models (4T1, 4T1.2) generated in athymic/immunodeficient mice.
- PIN-2 differentially elicits immune checkpoint inhibitors and cytokine therapies by enhancing peripheral innate immunity.

Objectives

1. Demonstrate immunomodulatory antitumor activity of PIN-2 either alone and in combination with other anticancer therapies.
2. Demonstrate generation of endogenous systemic-immune response in vivo (CD4+ tumor infiltrating lymphocytes (TILs)) in primary tumor.
4. PK & PE evaluation.

Methods & Results - in vivo & in vitro

Temporal administration of PIN-2 impacts tumor progression and increases survival

PIN-2 increases CD6+ cells in the spleen and primary tumor.

Overview of NGS

Differentially Expressed Genes (771 mRNAs)

Representative list of differentially expressed genes

Enriched GO Biological Processes of PIN-2 activity in human monocytes

Conclusions

- Potentiation and modulation of innate immunity is a frontline defense mechanism against advanced solid cancers that represents a therapeutic strategy to overcome cancer mediated immunosuppression.
- Dendritic cell-APCs are the master cellular regulators providing the essential link between innate & adaptive immunity - PIN-2 triggers the activation of monocyte-derived dendritic cells for presentation of a "tailored" profile of tumor-associated antigens unique to the individual.
- PIN-2 is a transactivating immunomodulator that stimulates APC’s via cellular penetration and subsequent regulation of cellular gene expression essential to the immune priming-phase and T-cell activation.
- PIN-2 demonstrates rapid-onset of immunomodulatory activity through activation of peripheral-blood mononuclear cells to promote CD6+ cytotoxic T lymphocyte maturation in the spleen and migration into primary tumors - Indicative of endogenous systemic immune response.
- Pharmacokinetic analysis demonstrated that PIN-2 was quickly cleared from the vascular compartment with a terminal half-life of 5.2 hours. PIN-2 was preferentially localized in peripheral blood mononuclear cells and spleen tissue.
- The immunodulatory effects of PIN-2 activity reveal molecular mechanisms and genetic pathways that traverse innate and adaptive immune signaling.
- PIN-2, a novel "Immunopriming" agent to enhance the immune system will be investigated in first-in-human clinical trials.